

**UNITED STATES DEPARTMENT OF COMMERCE****Patent and Trademark Offic**Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/610,215 07/05/00 GUNZBURG W 2316.2003-00

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 EXAMINER

DAVIS, K

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)
	09/610,215	GUNZBURG ET AL.
	Examiner	Art Unit
	Katharine F. Davis	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 05 July 2000.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-21 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 05 July 2000 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____.
5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6) <input type="checkbox"/> Other: _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4. | |

DETAILED ACTION

This Office Action is in response to the application filed on July 5, 2000. Claims 1-21 are pending in the instant application.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application 0005/98 filed in Denmark on January 6, 1998. It is noted, however, that applicant has not filed a certified copy of the Danish application as required by 35 U.S.C. 119(b).

Drawings

The drawing filed on July 5, 2000 has been approved by the draftsperson.

Information Disclosure Statement

Application docket numbers GSF9701A, GSF9703 and GSF9801 submitted with the IDS filed January 8, 2001 have been considered. Additionally, the search report from PCT/EP99/00002 has been considered.

Claim Objections

Claim 1 is objected to because of the following informality: Claim 1 recites the abbreviation "LTR" in line 2. An abbreviation should be defined upon first appearance in the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-21 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 19-21 provide for the use of a recombinant retroviral vector, the use of a recombinant retroviral vector system and the use of a retroviral particle respectively, for producing a pharmaceutical composition for gene therapy, but since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is

intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the phrase “...drive gene expression” in line 8. It is unclear exactly which genes the promoter is positioned to drive the expression of. Is the promoter driving the expression of the coding sequences inserted within the 3' LTR region or some other coding sequence?

Claim 4 recites the term “heterologous DNA” in line 2. It is unclear what the DNA is heterologous to (vector or cell?) thereby rendering the claim indefinite.

Claims 5, 10 and 18 recite the term “and/or”. This is considered to be improper Markush language because it is unclear what is actually encompassed by the claims thus rendering the claims indefinite.

Claim 6 recites the term “strong, constitutive promoter”. The metes and bounds of the term “strong” are unclear thereby rendering the claim indefinite.

Claim 10 is unclear as it does not recite a “second component” as is implied by the recitation of the “first component” in line 2.

Claim 18 recites the term “homologous and/or heterologous nucleotide sequences” in line 1. It is unclear what the nucleotide sequences are homologous and/or heterologous to thereby rendering the claim indefinite.

Claim 18 is incomplete. There is no positive process step which clearly relates back to the method recited in the preamble.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 16, 17 and 19-21 are drawn to a pharmaceutical composition comprising a recombinant retroviral particle and/or vector system for gene therapy.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The instant claims are broad in that they encompass a pharmaceutical composition that can be used in any gene therapy protocol to alleviate any disease and/or condition.

The nature of the invention is a method of gene therapy using a recombinant retroviral vector system.

The relative skill of those in the art of molecular biology, recombinant viral vectors and gene therapy is high.

An analysis of the prior art shows a lack of documented success for any treatment based on gene therapy. Verma *et al.* (Nature 389:239-242 1997) states that despite the more than 200 clinical trials underway, no successful outcome has been achieved. (see page 239, column 1, paragraph 2) The major obstacles to gene therapy are an inability to deliver genes efficiently to the target cell and to obtain sustained expression of the gene within the target cell. (see page 239, column 3, paragraph 2) Verma *et al.* concludes that although gene therapy holds enormous promise it is still a technique of the future. A better understanding of how to overcome the obstacles of gene delivery and expression are required before gene therapy can become a useful technique. (see page 242, columns 2 and 3) A year later, Anderson (Nature 392 Suppl:25-30 1998) lends support to the opinion of Verma *et al.* in stating "there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of human disease." (see page 25, column 1, paragraph 1) Palù *et al.* (J. Biotechnology 68:1-13 1999) further reiterates the opinion of Anderson and Verma *et al.* "...there is still no single outcome that undoubtedly showed a consistent benefit for the patient." (see abstract) Palù *et al.* concludes with "The main, real obstacle to the development of gene therapy as a powerful therapeutic tool remains the targeted and long-term regulated expression of the transgene." (see page 10, column 2, second paragraph and also Figure 1 on page 10). Furthermore, there are obstacles specific to the use of retroviral vectors in gene therapy protocols (see Verma *et al.* page 240, page 242, Table 2 and

Clinical Trials section; see also Anderson pages 25-27). Some of these obstacles are transducing non-dividing cells, sustaining long-term gene expression, safety issues (such as the possibility of producing replication-competent viruses, random integration into host DNA to possibly activate oncogenes or to inactivate tumor-suppressor genes, or to combine with endogenous retroviruses that exist in mammalian cells) and a cost-effective process to produce the vector (the vectors can only be produced by living cells).

While the prior art acknowledges the usefulness of gene therapy and the possibility of developing efficacious strategies in the future, it also illustrates that there are numerous obstacles to successful gene therapy which current methods still must overcome. As such, the disclosed utilities of the present specification which are drawn to gene therapy methods are credible. **The present rejection, therefore is not for lack of utility, but rather for lack of enablement for methods other than those limited to *in vitro* methods.**

The area of the invention is unpredictable. As discussed above, there is a lack of conclusive evidence that gene therapy protocols are successful in the treatment of human disease. Thus, the effectiveness of a new protocol can not be predicted in the absence of prior documented success of similar protocols.

The present specification provides little direction or guidance to support the claimed invention. The intended use for the claimed method is for the purpose of gene therapy. No direction as to how to overcome both the obstacles to gene therapy and the use of retroviral vectors for the purpose of gene therapy recognized by leaders in the field (as discussed above in the prior art section) is provided.

No working examples are disclosed wherein the claimed recombinant retroviral vector system is used in gene therapy protocols.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed recombinant retroviral vector system in gene therapy protocols. In order to determine how to use the claimed recombinant retroviral vector system in gene therapy protocols in order to prevent or treat human disease one of skill in the art would have to determine how to provide a therapeutic effect via a gene therapy protocol using the retroviral vector. The skilled artisan would have to determine optimized parameters for efficient gene delivery and sustained gene expression. The skilled artisan would also have to know how to overcome the problems specific to the use of retroviral vectors for gene therapy as discussed above in the prior art section of this rejection. Before the use of the claimed system for the treatment of human beings, one of skill in the art would need to be able to predict possible deleterious effects of treatment and ways to minimize or eliminate such effects. Since neither the prior art nor the present specification provides the answers to these questions it would require a large quantity of trial and error experimentation by the skilled artisan to answer these questions and successfully use the claimed invention.

Based on the broad scope of the claims, the nature of the invention, the skill of those in the art, the unpredictability of the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to use the claimed recombinant

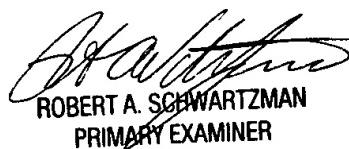
Art Unit: 1636

retroviral vector system in gene therapy protocols for the treatment of human disease. Therefore, the instant invention is not enabled for its intended use.

Conclusion

Claims 1-21 are rejected. Claims 1-21 are free of the prior art. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katharine F. Davis whose telephone number is (703) 605-1195 with direct desktop RightFax (703) 746-5199. The examiner can normally be reached on Monday-Friday (8:30am-5:00pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Schwartzman can be reached on (703) 308-7307. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications. Any inquiry concerning the formalities of this application should be directed to Patent Analyst Dianiece Jacobs whose telephone number is (703) 305-3388. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Katharine F. Davis
October 1, 2001



ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER